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NEWS 4 Jul 15 Data from 1960-1976 added to RDISCLOSURE
NEWS 5 Jul 21 Identification of STN records implemented
NEWS 6 Jul 21 Polymer class term count added to REGISTRY
NEWS 7 Jul 22 INPADOC: Basic index (/BI) enhanced; Simultaneous Left and
Right Truncation available
NEWS 8 AUG 05 New pricing for EUROPATFULL and PCTFULL effective
August 1, 2003
NEWS 9 AUG 13 Field Availability (/FA) field enhanced in BEILSTEIN
NEWS 10 AUG 15 PATDPAFULL: one FREE connect hour, per account, in
September 2003
NEWS 11 AUG 15 PCTGEN: one FREE connect hour, per account, in
September 2003
NEWS 12 AUG 15 RDISCLOSURE: one FREE connect hour, per account, in
September 2003
NEWS 13 AUG 15 TEMA: one FREE connect hour, per account, in
September 2003
NEWS 14 AUG 18 Data available for download as a PDF in RDISCLOSURE
NEWS 15 AUG 18 Simultaneous left and right truncation added to PASCAL
NEWS 16 AUG 18 FROSTI and KOSMET enhanced with Simultaneous Left and Right
Truncation
NEWS 17 AUG 18 Simultaneous left and right truncation added to ANABSTR
NEWS 18 SEP 22 DIPPR file reloaded

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TOTAL

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0.21 0.21

FILE 'REGISTRY' ENTERED AT 07:35:16 ON 24 SEP 2003
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STRUCTURE FILE UPDATES: ~~22 SEP 2003~~ HIGHEST RN 591204-55-6
DICTIONARY FILE UPDATES: ~~22 SEP 2003~~ HIGHEST RN 591204-55-6

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

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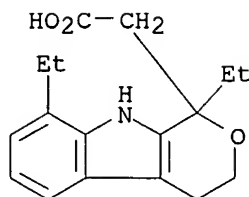
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s lodine/cn
L1 1 LODINE/CN

=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 41340-25-4 REGISTRY
CN Pyrano[3,4-b]indole-1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro- (9CI)
 (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Etodolac
CN (RS)-Etodolic acid
CN AY 24236
CN Edolan
CN Etodolac
CN Etodolic acid
CN **Lodine**
CN NIH 9918
CN NSC 282126
CN Ramodar
CN Tedolan
CN Ultradol
CN Zedolac
FS 3D CONCORD
DR 87226-38-8
MF C17 H21 N O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN,
 CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
 IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR,
 PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,
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Other Sources: DSL**, WHO
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5/4/41

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

537 REFERENCES IN FILE CA (1907 TO DATE)
 31 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 543 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file uspatfull
 COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
7.10	7.31

FULL ESTIMATED COST

FILE 'USPATFULL' ENTERED AT 07:36:48 ON 24 SEP 2003
 CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Sep 2003 (20030923/PD)
 FILE LAST UPDATED: 23 Sep 2003 (20030923/ED)
 HIGHEST GRANTED PATENT NUMBER: US6625813
 HIGHEST APPLICATION PUBLICATION NUMBER: US2003177560
 CA INDEXING IS CURRENT THROUGH 23 Sep 2003 (20030923/UPCA)
 ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Sep 2003 (20030923/PD)
 REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2003
 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2003

>>> USPAT2 is now available. USPATFULL contains full text of the original, i.e., the earliest published granted patents or applications. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. A USPATFULL record contains not only the original published document but also a list of any subsequent publications. The publication number, patent kind code, and publication date for all the US publications for an invention are displayed in the PI (Patent Information) field of USPATFULL records and may be searched in standard search fields, e.g., /PN, /PK, etc.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 41340-25-4/rn
 L2 185 41340-25-4/RN

=> s 12 and tablet and croscarmellose
63022 TABLET
2445 CROSCARMELLOSE
L3 9 L2 AND TABLET AND CROSCARMELLOSE

=> d 13 1-9

L3 ANSWER 1 OF 9 USPATFULL on STN
AN 2003:231677 USPATFULL
TI Fast dissolving tablets of cyclooxygenase-2 enzyme inhibitors
IN Murpani, Deepak, New Delhi, INDIA
Arora, Vinod Kumar, New Delhi, INDIA
Malik, Rajiv, New Delhi, INDIA
PI US 2003161875 A1 20030828
AI US 2002-85664 A1 20020227 (10)
DT Utility
FS APPLICATION
LN.CNT 373
INCL INCLM: 424/465.000
INCLS: 514/406.000
NCL NCLM: 424/465.000
NCLS: 514/406.000
IC [7]
ICM: A61K031-415
ICS: A61K009-20
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 2 OF 9 USPATFULL on STN
AN 2003:203149 USPATFULL
TI Modified release multiple-units compositions of non-steroid
anti-inflammatory drug substances (NSAIDs)
IN Skinh.o slashed.j, Annette, R.o slashed.dovre, DENMARK
Bertelsen, Poul, Vanlase, DENMARK
PA Nycomed Danmark A/S, Roskilde, DENMARK (non-U.S. corporation)
PI US 6599529 B1 20030729
WO 9912524 19990318
AI US 2000-508594 20000717 (9)
WO 1998-DK388 19980910
PRAI DK 1997-1044 19970911
DT Utility
FS GRANTED
LN.CNT 2701
INCL INCLM: 424/458.000
INCLS: 424/451.000; 424/457.000; 424/464.000; 424/468.000; 424/469.000;
424/470.000; 424/472.000; 424/474.000; 424/484.000; 424/489.000
NCL NCLM: 424/458.000
NCLS: 424/451.000; 424/457.000; 424/464.000; 424/468.000; 424/469.000;
424/470.000; 424/472.000; 424/474.000; 424/484.000; 424/489.000
IC [7]
ICM: A61K009-54
EXF 424/464; 424/468; 424/469; 424/470; 424/474; 424/484; 424/451; 424/452;
424/458; 424/472; 424/489
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 3 OF 9 USPATFULL on STN
AN 2003:176426 USPATFULL
TI Methods of treating headaches using 5-HT agonists in combination with
long-acting NSAIDs
IN Plachetka, John R., Chapel Hill, NC, United States
PA Pozen Inc., Chapel Hill, NC, United States (U.S. corporation)
PI US 6586458 B1 20030701
AI US 2000-559753 20000427 (9)

RLI Continuation-in-part of Ser. No. US 1998-151912, filed on 11 Sep 1998,
now patented, Pat. No. US 6060499 Division of Ser. No. US 1997-907826,
filed on 14 Aug 1997, now patented, Pat. No. US 5872145
Continuation-in-part of Ser. No. US 1999-253278, filed on 19 Feb 1999,
now abandoned

PRAI US 1996-24129P 19960816 (60)

DT Utility

FS GRANTED

LN.CNT 974

INCL INCLM: 514/415.000

INCLS: 514/449.000; 514/461.000; 514/473.000

NCL NCLM: 514/415.000

NCLS: 514/449.000; 514/461.000; 514/473.000

IC [7]

ICM: A61K031-405

EXF 514/449; 514/461; 514/473; 514/415

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 9 USPATFULL on STN

AN 2003:100144 USPATFULL

TI Pharmaceutical compositions for the coordinated delivery of NSAIDs

IN Plachetka, John R., Chapel Hill, NC, UNITED STATES

PA POZEN Inc. (U.S. corporation)

PI US 2003069255 A1 20030410

AI US 2002-158216 A1 20020531 (10)

PRAI US 2001-294588P 20010601 (60)

DT Utility

FS APPLICATION

LN.CNT 1200

INCL INCLM: 514/255.040

INCLS: 514/338.000; 514/406.000

NCL NCLM: 514/255.040

NCLS: 514/338.000; 514/406.000

IC [7]

ICM: A61K031-495

ICS: A61K031-4439; A61K031-415

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 9 USPATFULL on STN

AN 2003:92739 USPATFULL

TI SOLID CARRIERS FOR IMPROVED DELIVERY OF HYDROPHOBIC ACTIVE INGREDIENTS

IN PHARMACEUTICAL COMPOSITIONS

IN Patel, Mahesh V., Salt Lake City, UT, UNITED STATES

Chen, Feng-Jing, Salt Lake City, UT, UNITED STATES

PI US 2003064097 A1 20030403

US 6569463 B2 20030527

AI US 2001-800593 A1 20010306 (9)

RLI Division of Ser. No. US 1999-447690, filed on 23 Nov 1999, GRANTED, Pat.
No. US 6248363

DT Utility

FS APPLICATION

LN.CNT 3863

INCL INCLM: 424/465.000

NCL NCLM: 424/497.000

NCLS: 424/422.000; 424/427.000; 424/430.000; 424/433.000; 424/434.000;
424/435.000; 424/436.000; 424/441.000; 424/451.000; 424/457.000;
424/463.000; 424/464.000; 424/465.000; 424/466.000; 424/470.000;
424/474.000; 424/476.000; 424/482.000; 424/489.000; 424/490.000;
424/498.000; 514/773.000; 514/779.000; 514/784.000; 514/785.000;
514/786.000

IC [7]

ICM: A61K009-20

ICS: A61K009-16; A61K009-50
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 9 USPATFULL on STN
AN 2003:57971 USPATFULL
TI Treatment of migraine headache
IN Plachetka, John R., Chapel Hill, NC, UNITED STATES
Chowhan, Zakauddin T., Gaithersburg, MD, UNITED STATES
PA POZEN Inc. (U.S. corporation)
PI US 2003040537 A1 20030227
AI US 2002-255036 A1 20020926 (10)
RLI Division of Ser. No. US 2000-517751, filed on 3 Mar 2000, GRANTED, Pat.
No. US 6479551 Continuation-in-part of Ser. No. US 1997-966506, filed on
10 Nov 1997, GRANTED, Pat. No. US 6077539 Continuation-in-part of Ser.
No. US 1996-748332, filed on 12 Nov 1996, ABANDONED
PRAI WO 1997-US20611 19971112
DT Utility
FS APPLICATION
LN.CNT 1222
INCL INCLM: 514/406.000
INCLS: 514/619.000
NCL NCLM: 514/406.000
NCLS: 514/619.000
IC [7]
ICM: A61K031-415
ICS: A61K031-165

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 9 USPATFULL on STN
AN 2002:297630 USPATFULL
TI Treatment of migraine headache
IN Plachetka, John R., Chapel Hill, NC, United States
Chowhan, Zakauddin T., Gaithersburg, MD, United States
PA Pozen Inc., Chapel Hill, NC, United States (U.S. corporation)
PI US 6479551 B1 20021112
AI US 2000-517751 20000303 (9)
RLI Continuation-in-part of Ser. No. US 1997-966506, filed on 10 Nov 1997,
now patented, Pat. No. US 6077539 Continuation-in-part of Ser. No. US
1996-748332, filed on 12 Nov 1996, now abandoned
PRAI WO 1997-US20611 19971112
DT Utility
FS GRANTED
LN.CNT 1326
INCL INCLM: 514/619.000
INCLS: 424/451.000; 424/457.000; 424/458.000; 424/464.000; 424/468.000;
424/472.000; 514/406.000; 514/569.000; 514/570.000; 514/576.000;
514/577.000; 514/608.000; 514/617.000; 514/646.000; 514/709.000;
514/716.000; 514/717.000; 514/721.000; 514/964.000
NCL NCLM: 514/619.000
NCLS: 424/451.000; 424/457.000; 424/458.000; 424/464.000; 424/468.000;
424/472.000; 514/406.000; 514/569.000; 514/570.000; 514/576.000;
514/577.000; 514/608.000; 514/617.000; 514/646.000; 514/709.000;
514/716.000; 514/717.000; 514/721.000; 514/964.000
IC [7]
ICM: A61K031-16
ICS: A61K009-00; A61K031-00
EXF 514/406; 514/569; 514/570; 514/576; 514/577; 514/608; 514/617; 514/619;
514/646; 514/709; 514/716; 514/717; 514/721; 514/964; 424/468; 424/470;
424/472; 424/473; 424/474; 424/475; 424/480; 424/482; 424/451; 424/457;
424/458

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 8 OF 9 USPATFULL on STN
 AN 2001:93131 USPATFULL
 TI Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
 IN Patel, Mahesh V., Salt Lake City, UT, United States
 Chen, Feng-Jing, Salt Lake City, UT, United States
 PA Lipocine, Inc., Salt Lake City, UT, United States (U.S. corporation)
 PI US 6248363 B1 20010619
 AI US 1999-447690 19991123 (9)
 DT Utility
 FS GRANTED
 LN.CNT 3302
 INCL INCLM: 424/497.000
 INCLS: 424/422.000; 424/427.000; 424/430.000; 424/433.000; 424/434.000;
 424/435.000; 424/436.000; 424/441.000; 424/451.000; 424/457.000;
 424/463.000; 424/464.000; 424/465.000; 424/466.000; 424/470.000;
 424/474.000; 424/476.000; 424/482.000; 424/490.000; 424/489.000;
 424/498.000; 514/772.300; 514/773.000; 514/779.000; 514/784.000;
 514/785.000; 514/786.000
 NCL NCLM: 424/497.000
 NCLS: 424/422.000; 424/427.000; 424/430.000; 424/433.000; 424/434.000;
 424/435.000; 424/436.000; 424/441.000; 424/451.000; 424/457.000;
 424/463.000; 424/464.000; 424/465.000; 424/466.000; 424/470.000;
 424/474.000; 424/476.000; 424/482.000; 424/489.000; 424/490.000;
 424/498.000; 514/772.300; 514/773.000; 514/779.000; 514/784.000;
 514/785.000; 514/786.000
 IC [7]
 ICM: A61K009-16
 ICS: A61K009-28; A61K009-32; A61K009-52; A61K009-56; A61K009-58
 EXF 424/422; 424/433; 424/436; 424/435; 424/440; 424/451; 424/452; 424/464;
 424/465; 424/482; 424/489; 424/490; 424/480; 424/463; 424/470; 424/497;
 424/498; 424/476; 424/427; 424/430; 424/434; 424/441; 424/466; 424/474
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 9 OF 9 USPATFULL on STN
 AN 97:1191 USPATFULL
 TI Milled naproxen with hydroxypropyl cellulose as a dispersion stabilizer
 IN Franson, Nancy M., Collegeville, PA, United States
 Snyder, Donald R., Limerick, PA, United States
 PA NanoSystems L.L.C., Collegeville, PA, United States (U.S. corporation)
 PI US 5591456 19970107
 AI US 1995-386790 19950210 (8)
 DT Utility
 FS Granted
 LN.CNT 403
 INCL INCLM: 424/494.000
 INCLS: 424/493.000; 424/499.000; 514/781.000; 514/951.000
 NCL NCLM: 424/494.000
 NCLS: 424/493.000; 424/499.000; 514/781.000; 514/951.000
 IC [6]
 ICM: A61K009-18
 ICS: A61K009-14
 EXF 424/489; 424/494; 424/493; 424/499; 514/781; 514/951
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 13 1-9 ab, kwic

L3 ANSWER 1 OF 9 USPATFULL on STN
 AB The present invention relates to fast dissolving tablets for oral administration comprising a therapeutically effective amount of drug(s) that acts selectively as a cyclooxygenase-2 (COX-2) enzyme inhibitor,

which disintegrate quickly in mouth. The tablets are particularly suitable for patients who have difficulty in swallowing.

SUMM [0007] It is an object of the present invention to provide a fast dissolving **tablet** which comprises a therapeutically effective amount of drug(s) that acts as a cyclooxygenase-2 enzyme (COX-2) inhibitor for oral administration which. . . and dissolve in the oral cavity in less than about 30 seconds without the need of water. The fast dissolving **tablet** of COX-2 of the present invention process has pleasant mouth feel and there is no after taste or grittiness.

SUMM . . . can either be produced by conventional methods like wet granulation, dry granulation and direct compression or by specialized techniques like **tablet** molding and freeze drying.

SUMM . . . of floor space and labor as possible for a given operation, increasing attention is being given to direct compression of **tablet** preparation.

SUMM [0021] b) compressing the homogeneous mixture obtained in step (a) to form the fast dissolving **tablet** of COX-2 inhibitor.

SUMM . . . as microcrystalline cellulose, hydroxypropyl cellulose or carboxymethyl cellulose; alginates such as sodium alginate or alginic acid; cross-linked cellulose such as **croscarmellose** sodium; gums such as guar gum or xanthan gum; cross-linked polymers such as crospovidone; effervescent agent such as sodium bicarbonate. . .

SUMM . . . percent and most preferably about 2.0 weight percent of the COX-2 inhibitor compositions by this invention. The preferred disintegrant is **croscarmellose** sodium.

SUMM . . . of saccharin and dipeptide based sweeteners. The amount of sweetener will vary with the desired sweeteners selected for a particular **tablet** composition.

SUMM . . . in less than about 30 seconds preferably in about 25 seconds. The process of this invention for preparing rapidly dissolving **tablet** may be used for any strength of COX-2 inhibitor tablets without deviating from this invention.

DETD [0040]

Rofecoxib mouth dissolving tablets-25 mg.

Ingredient	Quantity (mg)
Rofecoxib	25.28
Aspartame	0.35
Mannitol	166.67
Croscarmellose sodium	4.00
Colloidal silicon dioxide	1.00
Mixed fruit flavour	0.70
Magnesium stearate	2.00
Total	200.00

DETD [0041] 1. Rofecoxib, aspartame, mannitol, **croscarmellose** sodium, colloidal silicon dioxide and mixed fruit flavour are sifted through the sieve #44 BSS and admixed for about 15. . .

DETD [0045]

Ingredient	Quantity (mg)
Rofecoxib	50.56
Aspartame	0.70
Mannitol	333.34
Croscarmellose sodium	8.0
Colloidal silicon dioxide	2.0
Mixed fruit flavour	1.4
Magnesium stearate	4.0

Total 400.0
 DETD [0047] The rofecoxib mouth dissolving **tablet** of 50 mg strength had an average weight of 400. \pm .20 mg, thickness of 4.9. \pm .0.2 mm, hardness of 4.5-5.0 Kp, disintegration. . .
 DETD [0048]

Nimesulide mouth dissolving **tablet**-100 mg.

Ingredient	Quantity (mg)
------------	---------------

Nimesulide	100.00
Aspartame	4.5
Mannitol	318.75
Croscarmellose sodium	10.5
Colloidal silicon dioxide	2.25
Orange flavour	4.5
Monosodium citrate	5.0
Magnesium stearate	4.5
Total	450.0

DETD [0050] The nimesulide mouth dissolving **tablet** of 100 mg strength had an average weight of 450. \pm .22.5 mg, thickness of 5.7. \pm .0.2 mm, hardness of 2-5 Kp, disintegration. . .

CLM What is claimed is:

1. A fast dissolving **tablet** which comprises a therapeutically effective amount of drug(s) that acts as a cyclooxygenase-2 (COX-2) inhibitor for oral administration.
2. The **tablet** according to claim 1 wherein the **tablet** comprises a therapeutically effective amount of COX-2 inhibitor, a filler and optionally, other pharmaceutical excipients.
3. The **tablet** according to claim 1 wherein the fast dissolving **tablet** dissolves in the mouth.
4. The **tablet** according to claim 1 or 2 wherein the drug(s) that acts as a cyclooxygenase-2 (COX-2) inhibitor is specific or preferential. . .
5. The **tablet** according to claim 4 wherein the COX-2 inhibitor is selected from the group consisting of meloxicam, rofecoxib, celecoxib, valdecoxib, parecoxib,. . .
6. The **tablet** according to claim 2 wherein the filler may be selected from the group consisting of alkali earth metal salts, carbohydrates,. . .
7. The **tablet** according to claim 9 wherein the filler may be selected from the group consisting of directly compressible dicalcium phosphate dihydrate,. . .
8. The **tablet** according to claim 2 wherein the pharmaceutical excipients comprises binders, disintegrants, lubricants, glidants, colouring agents, flavouring agents and sweeteners.
9. The **tablet** according to claim 8 wherein the binders may be selected from the group consisting of microcrystalline cellulose, mannitol, microcrystalline dextrose,. . .
10. The **tablet** according to claim 8 wherein the disintegrant is selected from the group consisting of starches or modified starches, clays, celluloses,. . .
11. The **tablet** according to claim 10 wherein the disintegrant is selected from the group consisting of sodium starch glycolate, corn starch, potato starch, pregelatinized starch, bentonite, montmorillonite, veegum, microcrystalline cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, alginic acid, **croscarmellose** sodium, guar gum, xanthan gum, crospovidone;

sodium bicarbonate and citric acid, and mixtures thereof.

12. The **tablet** according to claim 8 wherein the lubricants may be selected from the group consisting of talc, magnesium stearate, calcium stearate, . . .

13. The **tablet** according to claim 8 wherein the glidants may be selected from the group consisting of colloidal silicon dioxide and talc.

14. The **tablet** according to claim 8 wherein the colouring agents may be selected from any colorant used in pharmaceuticals which is approved. . .

15. The **tablet** according to claim 8 wherein the flavouring agent may be selected from the group consisting of natural and artificial flavours, . . .

16. The **tablet** according to claim 15 wherein the flavouring agent may be selected from the group consisting of peppermint, menthol, artificial vanilla, . . .

17. The **tablet** according to the claim 8 wherein the sweetener may be selected from the group consisting of natural and artificial sweeteners.

18. The **tablet** according to the claim 17 wherein the sweetener may be selected from the group consisting of monosaccharides, disaccharides, polysaccharides, partially. . .

19. The **tablet** according to the claim 18 wherein the sweetener may be selected from the group consisting of xylose, ribose, glucose, mannose, . . .

20. A mouth dissolving **tablet** of COX-2 inhibitor consisting of a COX-2 inhibitor, **croscarmellose** sodium, mannitol, aspartame, colloidal silicon dioxide, magnesium stearate and flavouring agent.

21. A process for preparing a fast dissolving **tablet** according to claim 2 comprising the steps of: (a) blending a therapeutically effective amount of COX-2 inhibitor, a filler, and. . .

IT 50-69-1, Ribose 50-70-4, Sorbitol, biological studies 50-99-7, Glucose, biological studies 57-48-7, Fructose, biological studies 57-50-1, Sucrose, biological studies 58-86-6, Xylose, biological studies 59-23-4, Galactose, biological studies 63-42-3, Lactose 69-65-8, Mannitol 69-79-4, Maltose 81-07-2D, Saccharin, salts 87-99-0, Xylitol 89-78-1, Menthol 89-83-8, Thymol 100-88-9D, Cyclamate, salts 119-36-8, Methyl salicylate 149-32-6, Erythritol 470-82-6, Eucalyptol 471-34-1, Calcium carbonate, biological studies 585-88-6, Maltitol 1305-62-0, Calcium hydroxide, biological studies 1343-88-0, Magnesium silicate 3458-28-4, Mannose 7757-93-9, Dicalcium phosphate 7758-87-4, Tricalcium phosphate 7778-18-9, Calcium sulfate 7789-77-7, Dicalcium phosphate dihydrate 9003-39-8, PVP 9004-34-6D, Cellulose, derivs. 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 9005-82-7, Amylose 9050-04-8, Calcium carboxy methyl cellulose 9050-36-6D, Maltodextrin, analogs 18996-35-5, Monosodium citrate 21645-51-2, Aluminum hydroxide, biological studies 22839-47-0, Aspartame 25322-68-3, Polyethylene glycol 39366-43-3, Aluminum magnesium hydroxide **41340-25-4**, Etodolac 42924-53-8, Nabumetone 51803-78-2, Nimesulide 64044-51-5, Lactose monohydrate 71125-38-7, Meloxicam 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 181695-72-7, Valdecoxib 198470-84-7, Parecoxib
(fast dissolving tablets of cyclooxygenase-2 inhibitors)

L3 ANSWER 2 OF 9 USPATFULL on STN

AB An oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance to

obtain both a relatively fast onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time is disclosed.

SUMM . . . release part of the composition is intended to release the drug substance in a manner which corresponds to a plain **tablet** formulation or the like and the term "immediate" is in such a context intended to denote that the release of. . .

SUMM . . . fast disintegration time but not necessarily a suitable dissolution rate of the drug substance under acidic conditions, i.e. a plain **tablet** will rapidly disintegrate into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under. . .

SUMM Based on the knowledge of the pharmacokinetics of lornoxicam and a study performed by us employing a plain **tablet** and a solution (Hitzenberger G, Radhofer-Welte S, Takacs F, Rosenow D.: Pharmacokinetics of lornoxicam in man, Postgrad. Med. J. 1990,. . .

SUMM . . . similar to the plasma concentration obtained 8-12 hours after administration of half the dose in the form of a plain **tablet**),

SUMM . . . not be higher than the peak concentration observed after administration of half the dose in the form of a plain **tablet**, and

SUMM . . . were that the daily dose of lornoxicam is the same irrespective of whether a once daily composition or a plain **tablet** or a solution were administered,

SUMM i) that a plain **tablet** will remain in the stomach for about 1 hour before a passage into the intestine takes place (estimated from the difference in T.sub.max between the solution (0.5 hours) and the plain **tablet** (1.5 hour),

SUMM . . . when different dosages are administered together as the load of active ingredient may differ depending on the size of the **tablet** . The release profile for 100 mg given in a single dosage may thus differ from 100 mg given as 5. . .

SUMM The preferred dosage form according to the invention is in the form of a capsule, **tablet**, sachet etc. The size of the dosage form is adapted to the amount of the NSAID substance of the composition.

SUMM The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, **tablet**, a sachet or any other relevant dosage form known within the art. A dosage unit represents a plurality of individual. . . units which in accordance with the general state of the art may be in the form of a capsule, a **tablet**, a sachet, etc.

SUMM . . . the units, typically more than 100, a sachet containing a multiplicity of the units, typically more than 1000, or a **tablet** made from a multiplicity of the units, typically more than 100, in such a manner that the **tablet** will disintegrate substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout. . .

SUMM . . . a multiplicity of individual units. The dosage unit form is preferably a solid dosage unit form such as, e.g., a **tablet**, a capsule, or a sachet, especially in the form of capsules.

SUMM . . . cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; **croscarmellose** sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol.RTM.); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon.RTM. CL, Polyvidon.RTM. CL-M, Kollidon.RTM.. . .

DETD . . . E 5 Premium) Ph.Eur. Dow

Magnesii stearas Ph.Eur. Akcros Chemicals

Talcum Ph.Eur. Whittaker, Clark and

Daniels

Eudragit NE 30 D Ph.Eur. Rohm Pharma GmbH

Croscarmellose sodium (Ac-Di-Sol) Ph.Eur. FMC
Dibasic Calcium Phosphate, Anhydrous USPNF Kyowa
(Calcium hydrogen phosphate, mean
particle size approx. 30 .mu.m)
Sodium bicarbonate USPNF Kirsch
(sodium hydrogencarbonate, . . .

DETD . . . 27

III Cellulose, microcrystalline 51

IV Lactose 142.5

V Carmellose sodium 1.5

VI Maltodextrin 6

VII Pregelatinized starch 30

VIII **Croscarmellose** sodium 15

IX Purified water 51 + 15 + 15

DETD . . . is released at a pH corresponding to that of 0.07 N HCl. The inclusion of an disintegrant such as, e.g., **croscarmellose** sodium does not seem to have any increasing effect on the release rate of lornoxicam from the pellet cores. Furthermore, . . .

DETD The dissolution of **tablet** cores was determined by the dissolution method II (0.07 N HCl) and is as follows:

DETD Batch No. 26089831: 500 .mu.m sieved granulate in an amount corresponding to a 150 mg **tablet**. In the following is given the results from the dissolution test.

DETD Batch No. 26089831: 1000 .mu.m sieved granulate in an amount corresponding to a 150 mg **tablet**. In the following is given the results from the dissolution test.

CLM What is claimed is:

. . . The composition according to claim 1, wherein the unit dosage of the composition is in the form of a capsule, **tablet** or sachet.

IT 50-33-9, Phenylbutazone, biological studies 50-78-2, Acetylsalicylic acid 52-67-5, Penicillamine 53-86-1, Indomethacin 59-05-2, Methotrexate 61-68-7, Mefenamic acid 103-90-2, Paracetamol 599-79-1, Sulfasalazine 5104-49-4, Flurbiprofen 13710-19-5, Tolfenamicacid 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 22071-15-4, Ketoprofen 22204-53-1, Naproxen 26171-23-3, Tolmetin 29679-58-1, Fenoprofen 33005-95-7, Tiaprofenic acid 34031-32-8, Auranofin 36322-90-4, Piroxicam 36330-85-5, Fenbufen 38194-50-2, Sulindac **41340-25-4**, Etodolac 42924-53-8, Nabumetone 51146-56-6, Dexibuprofen 51481-61-9, Cimetidine 51803-78-2, Nimesulide 53164-05-9, Acemetacin 57132-53-3, Proglumetacin 59122-46-2, Misoprostol 59804-37-4, Tenoxicam 65847-85-0, Morniflumate 66357-35-5, Ranitidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 73590-58-6, Omeprazole 89796-99-6, Aceclofenac 102625-70-7, Pantoprazole 103577-45-3, Lansoprazole (modified-release multiple-units compns. of non-steroid anti-inflammatory drugs)

L3 ANSWER 3 OF 9 USPATFULL on STN

AB The invention is directed to methods and compositions that can be used in the treatment of headaches. In particular, methods and compositions are described involving the combination of a long-acting NSAID and a 5-HT agonist. Included among the long-acting NSAIDs are cyclo-oxygenase-2 inhibitors.

SUMM H. "Unit dosage form" shall mean a single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee, suppository, or syringe combining both a 5-HT agonist and an NSAID would be a unit dosage. . . .

SUMM I. "Quick dissolve" in reference to a **tablet** or other oral dosage form shall mean that the oral dosage form is at least 95% dissolved within 20 minutes. . . .

DETD . . . attack consisting of typical migraine headache, nausea and

sensitivity to light and sound. She is dosed with a single oral **tablet** containing sumatriptan 25 mg and naproxen sodium 550 mg. Her symptoms start to diminish within one hour and by three. . .

DETD . . . She is dosed with a single subcutaneous injection of sumatriptan 6 mg and at the same time orally ingests a **tablet** containing naproxen sodium 550 mg. Her symptoms start to diminish within 20 minutes and by two hours she is completely. . .

DETD . . . attack consisting of typical migraine headache, nausea and sensitivity to light and sound. She is dosed with a single oral **tablet** containing 12.5 mg sumatriptan and 550 mg naproxen sodium. Her symptoms start to diminish within one hour. By three hours. . .

DETD . . . to light and sound. She is dosed with a single subcutaneous injection of 2 mg sumatriptan and orally ingests a **tablet** containing 550 mg naproxen sodium. Her symptoms start to diminish within 30 minutes and by two hours she is completely. . .

DETD . . . age offers the same presenting history and indication as in Example 1. Treatment is by means of a single oral **tablet** containing 50 mg sumatriptan and 550 mg naproxen. The same result as in Example 1 is obtained.

DETD A variety of combinations of 5-HT agonists and NSAIDs can be made into a single dosage form, either **tablet**, capsule, suppository, parenteral or other. As an example, a rapidly dissolving **tablet** of 0.5 mg ergotamine tartrate combined with 550 mg naproxen sodium is conveniently available for use. Another example includes a rapidly dissolving **tablet** of 12.5 mg of sumatriptan combined with 550 mg of naproxen sodium. Other agents may also be present such as: pregelatinized maize starch, polyvinyl-pyrrolidone or hydroxypropyl methylcellulose; fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); disintegrants (e.g., potato starch, **croscarmellose** sodium, or sodium starch glycolate); wetting agents (e.g., sodium lauryl sulphate) or other agents for tableting.

DETD . . . be made up of various agents listed herein. As an example, in the case of naproxen sodium and sumatriptan, several **tablet** strengths are available including: 12.5 mg sumatriptan/550 mg naproxen sodium; 25 mg sumatriptan/550 mg naproxen sodium; 12.5 mg sumatriptan/275 mg naproxen sodium; and 25 mg sumatriptan/275 mg naproxen sodium. Each **tablet** dissolves within 20 minutes to rapidly produce effective blood levels of each component.

IT 53-86-1, Indomethacin 61-68-7, Mefenamic acid 5104-49-4, Flurbiprofen 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22204-53-1D, Naproxen, salts 26159-34-2, Naproxen sodium 36322-90-4, Piroxicam **41340-25-4**, Etodolac 42924-53-8, Nabumetone 74103-06-3, Ketorolac

(long-acting NSAID; treatment of migraine headaches with 5-HT agonists in combination with long-acting NSAIDs)

L3 ANSWER 4 OF 9 USPATFULL on STN

AB The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of treating patients by administering this coordinated release, gastroprotective, antiarthritic/analgesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

SUMM . . . The term "unit dosage form" as used herein refers to a single entity for drug administration. For example, a single **tablet** or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. A unit dosage form. . . after the pH in the GI tract has risen. In a preferred embodiment, the unit dosage form is a multilayer

tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred. . .

SUMM . . . unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer **tablet** having an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

DRWD [0017] FIG. 1 is a schematic diagram of a four layer **tablet** dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the. . .

DETD . . . al. (Jpn. J. Pharmacol. 78:365-371 (1998)) and Panara, et al. (Br. J. Pharmacol. 116:2429-2434 (1995)). The amount present in a **tablet** or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example:

DETD [0036] Celecoxib may be administered in a **tablet** or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200. . .

DETD [0045] The Making of **Tablet** Dosage Forms

DETD . . . Preferably, the combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer **tablet**. In a bilayer configuration, one portion of the **tablet** contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the **tablet** will contain the NSAID, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In. . .

DETD [0048] A schematic diagram of a four layer **tablet** dosage form is shown in FIG. 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable. . .

DETD . . . conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core **tablet** weight. In particular embodiments, the core naproxen sodium **tablet** is coated with coating ingredients such as Opaspray.RTM. K-1-4210A or Opadry.RTM. YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients. . .

DETD . . . aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/ Tablet
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP. . .		

DETD . . . adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/
Tablet		
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25
Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		

Enteric Coating Dispersion Ingredients	% W/W
--	-------

Methacrylic Acid Copolymer. . .

DETD [0056] A trilayer **tablet** which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core **tablet** of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. 2 shows an example of an appropriate trilayer **tablet**. In this particular example, naproxen is mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, . . .

DETD [0057] The controlled-release core **tablet** of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay. . .

DETD . . . contains Opadry Blue.RTM. YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core **tablet**. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray.RTM. K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core **tablet** are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;. . . adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/
Tablet		
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9
Magnesium Stearate, NF	1.00	7.95
Total	100.00	797.85

Enteric Coating Dispersion Ingredients % . . .

DETD [0060] A trilayer **tablet** which separates famotidine contained in the film coat from controlled-release naproxen and famotidine may be used in the present invention. The core **tablet** of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. FIG. 2 is an example of an appropriate trilayer **tablet**. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules. . .

DETD [0061] The controlled-release core **tablet** of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is. . .

DETD . . . contains Opadry Blue.RTM. YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core **tablet**. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray.RTM. K-1-4210A (Colorcon, West Point, Pa.) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core **tablet** are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;. . . adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/
--------------------------------	-------	-----

Tablet

Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose	7.03	39.9
2208, USP (viscosity 15000 cps)		
Magnesium Stearate, NF	1.40	7.95
Total	100.00	567.85

Enteric Coating. . .

DETD [0064] A schematic diagram of a four layer **tablet** dosage form is shown in FIG. 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable. . .

DETD . . . conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core **tablet** weight. In particular embodiments, the core naproxen sodium **tablet** is coated with coating ingredients such as Opaspray.RTM. K-1-4210A or Opadry.RTM. YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients. . .

DETD . . . by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core **tablet** weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as. . . releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core **Tablet** Ingredients % W/W mg/**tablet**

Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP. . .		

DETD . . . slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the **tablet** cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric. . .

DETD . . . and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the **tablet** bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if. . .

DETD . . . clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the **tablet** cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

DETD [0073] A schematic diagram of a four layer **tablet** dosage form is shown in FIG. 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable. . .

DETD . . . conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core **tablet** weight. In particular embodiments, the core naproxen sodium **tablet** is coated with coating ingredients such as Opaspray.RTM. K-1-4210A or Opadry.RTM. YS-1-7006 (Colorcon, West Point, Pa.). Polymer film coating ingredients. . .

DETD . . . by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core **tablet** weight. Other

ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as. . . omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	% W/W	mg/tablet
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Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP. . . .		

DETD . . . slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the **tablet** cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

DETD . . . and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the **tablet** bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is. . .

DETD . . . clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the **tablet** cores in a conventional coating pan until proper amount of omeprazole is deposited on the tablets.

DETD . . . formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
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Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00.	. . .

DETD . . . delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and **croscarmellose** sodium as a disintegrant. Naproxen pellets as shown in FIG. 3 do not need a subcoating layer and are enteric. . . these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer **tablet**

Omeprazole Granules	% W/W	mg/capsule
---------------------	-------	------------

Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium laurylsulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

DETD . . . formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/ tablet
Naproxen, USP	76.22	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.78	71.44
Povidone (K90), USP	2.00	6.56
Total	100.00	328.00

CLM

What is claimed is:

12. The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer **tablet**.

13. The pharmaceutical composition of claim 12, wherein said unit dosage form is a trilayer **tablet** having an outer layer of said acid inhibitor and an inner core of said NSAID.

14. The pharmaceutical composition of claim 12, wherein said unit dosage form is a bilayer **tablet** having an outer layer of said acid inhibitor and an inner core of said NSAID.

15. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of. . .

16. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of. . .

17. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of. . .

18. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said. . .

19. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said. . .

20. The pharmaceutical composition of any one of claims 12-14, wherein said **tablet** has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said. . .

36. The method of claim 35, wherein said single dosage form is a bilayer **tablet** with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

49. The method of claim 48, wherein said single dosage form is a bilayer **tablet** with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

IT

50-78-2, Aspirin 53-86-1, Indomethacin 103-90-2, Acetaminophen
5104-49-4, Flurbiprofen 15687-27-1, Ibuprofen 21256-18-8, Oxaprozin
22071-15-4, Ketoprofen 36322-90-4, Piroxicam **41340-25-4**,
Etodolac 42924-53-8, Nabumetone 51481-61-9, Cimetidine 66357-35-5,
Ranitidine 70374-39-9, Lornoxicam 71125-38-7, Meloxicam 73590-58-6,
Omeprazole 74103-06-3, Ketorolac 76956-02-0, Loxitidine 100981-43-9,
Ebrotidine 102625-70-7, Pantoprazole 103577-45-3, Lansoprazole
117976-89-3, Rabeprazole 118288-08-7, Lafutidine 119141-88-7,
EsOmeprazole 123653-11-2, NS 398 138786-67-1, Pantoprazole sodium
158205-05-1, L-745337 162011-90-7, Rofecoxib 169590-42-5, Celecoxib
180200-68-4, JTE-522 181695-72-7, Valdecoxib 198470-84-7, Parecoxib
202409-33-4, Etoricoxib 346670-87-9, CS 502 (pharmaceutical)
(pharmaceutical compns. for coordinated delivery of NSAIDs)

L3 ANSWER 5 OF 9 USPATFULL on STN

AB The present invention provides solid pharmaceutical compositions for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compositions of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutrionals, cosmeceuticals and diagnostic agents.

DETD . . . bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a minitab^{let}, a **tablet** or a capsule. A powder constitutes a finely divided (milled, micronized, nanosized, precipitated) form of an active ingredient or additive. . . .

DETD [0174] disintegrants or super disintegrants, such as **croscarmellose** sodium, starch, starch derivatives, clays, gums, cellulose, cellulose derivatives, alginates, crosslinked polyvinypyrrolidone, sodium starch glycolate and microcrystalline cellulose;

DETD . . . other processes known in the art. The compositions can be provided in the form of a minicapsule, a capsule, a **tablet**, an implant, a troche, a lozenge (minitab^{let}), a temporary or permanent suspension, an ovule, a suppository, a wafer, a chewable **tablet**, a quick or fast dissolving **tablet**, an effervescent **tablet**, a buccal or sublingual solid, a granule, a film, a sprinkle, a pellet, a bead, a pill, a powder, a. . . .

DETD . . . or otherwise added to the carrier or composition. The coating may be applied to a compressed or molded or extruded **tablet**, a gelatin capsule, and/or pellets, beads, granules or particles of the carrier or composition. The coating may be applied through. . . .

DETD . . . effect release in the lower gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded **tablet**/mold (coated or uncoated) containing granules, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves. . . .

DETD . . . (morphology, particle size distribution, polymorphism and dissolution characteristics) of spray congealed pellets. The spray congealed particles may be used in **tablet** granulation form, encapsulation form, or can be incorporated into a liquid suspension form.

CLM What is claimed is:

. . . pellet, a bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a **tablet** or a capsule.

29. The pharmaceutical composition of claim 1 in the form of a capsule, a **tablet**, an ovule, a suppository, a wafer, a chewable **tablet**, a buccal **tablet**, a sub-lingual **tablet**, a quick-dissolve **tablet**, an effervescent **tablet**, a granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitut^{able} solid,. . . .

44. The pharmaceutical composition of claim 34 in the form of a capsule, a **tablet**, an ovule, a suppository, a wafer, a chewable **tablet**, a buccal **tablet**, a sub-lingual **tablet**, a quick-dissolve **tablet**, an effervescent **tablet**, a

granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry
syrup, a reconstitutable solid, . . .

74. The pharmaceutical composition of claim 49 in the form of a capsule,
a **tablet**, an ovule, a suppository, a wafer, a chewable
tablet, a buccal **tablet**, a sub-lingual **tablet**

, a quick-dissolve **tablet**, an effervescent **tablet**, a
granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry
syrup, a reconstitutable solid, . . .

87. The pharmaceutical composition of claim 79 in the form of a capsule,
a **tablet**, an ovule, a suppository, a wafer, a chewable
tablet, a buccal **tablet**, a sub-lingual **tablet**

, a quick-dissolve **tablet**, an effervescent **tablet**, a
granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry
syrup, a reconstitutable solid, . . .

IT 50-14-6, Ergocalciferol 50-21-5D, Lactic acid, glycerides 50-24-8,
Prednisolone 50-28-2, EStradiol, biological studies 50-70-4,
Sorbitol, biological studies 51-48-9, L-Thyroxine, biological studies
52-01-7, Spironolactone 55-98-1, Busulphan 56-81-5,
1,2,3-Propanetriol, biological studies 56-81-5D, Glycerol, polyethylene
fatty acid esters 57-10-3, Hexadecanoic acid, biological studies
57-11-4, Octadecanoic acid, biological studies 57-55-6,
1,2-Propanediol, biological studies 57-55-6D, Propylene glycol, ethers
57-83-0, Progesterone, biological studies 57-88-5, Cholesterol,
biological studies 57-88-5D, Cholesterol, polyoxyethylene derivs.
60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies
64-17-5, Ethanol, biological studies 66-76-2, Dicoumarol 67-20-9,
Nitrofurantoin 67-45-8, Furazolidone 67-63-0, Isopropanol, biological
studies 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol
69-65-8, Mannitol 71-36-3, Butanol, biological studies 76-57-3,
Codeine 76-99-3, Methadone 77-89-4, Acetyl triethylcitrate 77-90-7,
Acetyl tributyl citrate 77-92-9D, Citric acid, diglycerides 77-93-0,
Triethylcitrate 77-94-1, Tributylcitrate 81-24-3 81-25-4 83-44-3
87-33-2, Isosorbide dinitrate 87-69-4D, Tartaric acid, glycerides,
biological studies 90-82-4, Pseudoephedrine 100-51-6,
Benzenemethanol, biological studies 102-76-1, Triacetin 104-31-4,
Benzonate 105-37-3, Ethyl propionate 105-54-4, Ethyl butyrate
105-60-2, biological studies 105-60-2D, Caprolactam, N-Alkyl derivs.
106-32-1, Ethyl caprylate 107-21-1, 1,2-Ethenediol, biological studies
110-27-0, Isopropyl myristate 111-03-5, Glyceryl monooleate 111-62-6,
Crodamol EO 111-90-0, Transcutol 112-80-1, 9-Octadecenoic acid (9Z)-,
biological studies 113-15-5, Ergotamine 113-92-8, Chlorpheniramine
115-77-5, biological studies 115-83-3, Pentaerythrityl Tetra stearate
124-07-2, Octanoic acid, biological studies 125-84-8, Aminoglutethimide
126-07-8, Griseofulvin 127-19-5, Dimethylacetamide 128-13-2
141-22-0 142-18-7, Glyceryl monolaurate 142-62-1, Hexanoic acid,
biological studies 142-91-6, Isopropyl palmitate 143-07-7, Dodecanoic
acid, biological studies 151-41-7, Lauryl sulfate 155-97-5,
Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide
298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amphetamine
302-79-4, Tretinoin 303-49-1, Clomipramine 321-64-2, Tacrine
334-48-5, Decanoic acid 359-83-1, Pentazocine 360-65-6 378-44-9,
Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1,
Metronidazole 463-40-1 474-25-9 475-31-0 511-12-6,
Dihydroergotamine 516-35-8 516-50-7 520-85-4, Medroxyprogesterone
542-28-9, .delta.-Valerolactone 544-35-4, Ethyl linoleate 544-63-8,
Tetradecanoic acid, biological studies 577-11-7, Sodium docusate
595-33-5 616-45-5, Pyrrolidone 616-45-5D, Pyrrolidone, N-Alkyl
derivs. 623-84-7, Propylene glycol diacetate 640-79-9 675-20-7,
2-Piperidone 872-50-4, N-Methylpyrrolidone, biological studies
1134-47-0, Baclofen 1331-12-0, Propylene glycol monoacetate
1335-71-3, Propylene glycol oleate 1338-39-2, Arlacel 20 1338-43-8,
Span 80 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4,

Vitamin E 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 2687-91-4, N-Ethylpyrrolidone 2687-94-7 2687-96-9 3068-88-0, .beta.-Butyrolactone 3445-11-2 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 5306-85-4, Dimethyl isosorbide 7261-97-4, Dantrolene 7488-99-5, .alpha. Carotene 7664-93-9D, Sulfuric acid, salts alkyl derivs., biological studies 7689-03-4, Camptothecin 8007-43-0, Sorbitan sesquioleate 9002-89-5, Polyvinylalcohol 9002-92-0, Brij 30 9002-96-4 9003-39-8, Polyvinylpyrrolidone 9004-65-3, Hydroxypropyl methylcellulose 9004-74-4, Methoxy polyethylene glycol 9004-81-3, Polyoxyethylene laurate 9004-95-9, Polyoxyethylene cetyl ether 9004-96-0, PEG-32 oleate 9004-98-2, Polyoxyethylene oleyl ether 9004-99-3, Polyoxyethylene stearate 9005-00-9, Polyoxyethylene stearyl ether 9005-02-1, Polyoxyethylene dilaurate 9005-07-6, Polyoxyethylene dioleate 9005-08-7, Polyoxyethylene distearate 9005-32-7D, Alginic acid, salts 9005-37-2, Propylene glycol alginate 9005-63-4D, Polyoxyethylene sorbitan, derivs. 9005-63-4D, Polyoxyethylene sorbitan, fatty acid esters 9005-64-5, Tween 20 9005-65-6, Polysorbate 80 9005-66-7, Tween 40 9005-67-8, Tween 60 9007-48-1, PLUROLIOLEIQUECC497 9011-21-6, Polyoxyethylene glyceryl stearate 9016-45-9 9036-19-5 10238-21-8, Glyburide 10540-29-1, Tamoxifen 11103-57-4, Vitamin A 11140-04-8, Imwitor 988 12001-79-5, Vitamin K 12619-70-4, Cyclodextrin 12619-70-4D, Cyclodextrin, derivs. 12619-70-4D, Cyclodextrin, hydroxypropyl ethers 13081-97-5, Pentaerythrityl di stearate 14440-80-3, Stearoyl-2-lactylate 14605-22-2 15307-86-5, Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 15687-27-1, Ibuprofen 18559-94-9, Albuterol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22882-95-7, Isopropyl linoleate 22916-47-8, Miconazole 23288-49-5, Probuco1 25168-73-4, Sucrose monostearate 25265-75-2, Butanediol 25322-68-3 25322-69-4, Polypropylene glycol 25339-99-5, Sucrose monolaurate 25523-97-1, Dexchlorpheniramine 25618-55-7D, Polyglycerol, fatty acid esters 25637-84-7, Glyceryl dioleate 25637-97-2, Sucrose dipalmitate 25812-30-0, Gemfibrozil 26266-57-9, Sorbitan monopalmitate 26266-58-0, Sorbitan Trioleate 26402-22-2, Glyceryl monocaprate 26402-26-6, Glyceryl monocaprylate 26446-38-8, Sucrose monopalmitate 27154-43-4D, Piperidone, N-Alkyl derivs. 27195-16-0, Sucrose distearate 27203-92-5, TRamadol 27638-00-2, Glyceryl dilaurate 29094-61-9, Glipizide 29767-20-2, Teniposide 31692-85-0, Glycofuro1 32222-06-3, Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34911-55-2, Bupropion 36354-80-0, Glyceryl dicaprylate 37321-62-3, Lauroglycol 38304-91-5, Minoxidil 41340-25-4, Etodolac 42924-53-8, Nabumetone 43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 51333-22-3, Budesonide 51481-61-9, Cimetidine 51938-44-4, Sorbitan sesquisteate 52581-71-2, Volpo 3 53123-88-9, Sirolimus 53168-42-6, Myvacet 9-45 53179-11-6, Loperamide 53230-10-7, Mefloquine 53988-07-1, Glyceryl dicaprate 54392-26-6, Sorbitan monoisostearate 54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine 57107-97-8, Polyoxyethylene glyceryl oleate 59467-70-8, Midazolam 59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61379-65-5, Rifapentine 61869-08-7 62013-04-1, Dirithromycin 62356-64-3 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin (pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

L3 ANSWER 6 OF 9 USPATFULL on STN

AB The invention is directed to pharmaceutical compositions useful in the treatment of migraine. The compositions contain metoclopramide and one or more NSAIDs in unit dosage form. By selecting NSAIDs that are

non-acidic or segregating the metoclopramide and NSAID, the storage life of the compositions has been increased. Also disclosed are coordinated dosage forms for the sequential release of drugs. The invention encompasses methods of treating migraine using any of these dosage forms.

SUMM . . . non-acidic NSAID) in an amount effective to reduce or eliminate headache pain. Preferably, the dosage form should be either a **tablet** or capsule and should be free from vasoactive agents, including 5 HT agonist vasoactive agents. The dosage form may be. . .

SUMM . . . which either metoclopramide or analgesic is barrier coated. Alternatively, metoclopramide and analgesic may be in separate layers of a multilayer **tablet**. Dosage forms should typically be free of vasoactive agents, may be coordinated and may contain either long-acting NSAIDs or NSAIDs. . .

SUMM . . . (1999), ISBN: 0471148288). Coordinated dosage forms should be suitable for oral delivery and will typically take the form of a **tablet** or capsule. Metoclopramide and NSAID may be in separate layers of a multilayer **tablet** and, in general, these dosage forms should be substantially free of vasoactive agents such as 5 HT agonists.

SUMM . . . be acid-base storage stabilized or coordinated and should, preferably, be suitable for oral administration (e.g. in the form of a **tablet** or capsule). It will also generally be advantageous for metoclopramide to be present at a concentration effective to reduce or.

DRWD [0017] FIG. 4. is a comparative dissolution plot of the metoclopramide presented in a **tablet** coating layer and presented in a compressed **tablet** layer.

DRWD [0018] FIG. 5a is a plot of plasma concentrations of metoclopramide upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD [0019] FIG. 5b is a plot of plasma concentrations of naproxen sodium upon administration of **tablet**(s) of the present invention as disclosed in **Tablet** Example 4.

DRWD [0020] FIG. 6 is a diagrammatic cross section side view of a **tablet** coating pan with baffles and spray nozzles.

DETD . . . that serves as a barrier to prevent interaction of the drugs may be segregated into different layers of a multilayer **tablet**. Methods for producing "acid-base storage stabilized" dosage forms are described in the Examples section below. Such dosage forms may, of. . .

DETD [0030] The Making of **Tablet** Dosage Forms

DETD [0031] The combination of metoclopramide and an analgesic may take place in a single layer **tablet** or other solid dosage form. A bi- or multi layer **tablet** of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the. . .

DETD [0032] In a bilayer configuration, one portion of the **tablet** contains metoclopramide in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc., and is, preferably, designed. . . the naproxen (or other analgesic) to the small intestine which is the site of most rapid absorption. In a bilayer **tablet** embodiment, the second portion of the **tablet** will contain, preferably, naproxen sodium in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. It. . .

DETD [0033] In one embodiment of bilayer **tablet** preparation, once the two components have been manufactured, they are combined into a single **tablet**. This process allows for different dosages of either component (i.e. the metoclopramide component or the naproxen sodium component) to be usefully combined into a single **tablet** in an efficient way. In another embodiment, substantially each naproxen

sodium crystal (or metoclopramide particle) is coated with a rapid. .

DETD [0034] Powder flow characteristics and powder compressibility are the main criteria to be considered with respect to successful **tablet** production. To improve compressibility, naproxen sodium may be granulated. This involves increasing granule size through the addition of excipients that. . .

DETD . . . forms should be used, e.g., the acidic analgesic and the metoclopramide may be sequestered to different layers of a multilayer **tablet** in such a manner that contact between the drugs is eliminated or minimized. In the case of COX-2 inhibitors, the. . .

DETD . . . al., Jpn. J. Pharmacol. 78:365-371 (1998); and Panara, et al., Br. J. Pharmacol. 116:2429-2434 (1995). The amount present in a **tablet** or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example, piroxicam may be present at 10 to 20 mg per **tablet**. Celecoxib may be administered to a human in an amount of from about 100 mg to about 500 mg or. . .

DETD [0064] N. "Unit dosage form" shall mean single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee (oral unit dosage forms), suppository, or syringe combining both metoclopramide and an NSAID would be a. . .

DETD . . . levels of metoclopramide. The data was obtained from 10 healthy volunteer subjects. On day 1, the subjects were administered one **tablet** of 500 mg naproxen sodium and 8 mg metoclopramide prepared as described in the Examples section. On day 4, two. . .

DETD Example 1: **Tablet** Formulation #1

DETD [0071] A variety of combinations of metoclopramide and analgesic can be made into a single dosage form (e.g., **tablet**, capsule, suppository) consisting of one or more layers. In this example, a sequentially and rapidly dissolving single layer **tablet** of metoclopramide, 8 mg, is combined with naproxen sodium, 500 mg. Referring to FIG. 1, this single layer **tablet** contains naproxen sodium in crystalline form (2) and metoclopramide (4), each uniformly distributed throughout a matrix (6) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "carrier material"). A pharmaceutically acceptable **tablet** coating (8) surrounds the active ingredients and carrier materials. Carrier material should be present in an amount of between 50 and 2000 mg, and preferably between 500 and 1,000 mg. Prior to compaction in a **tablet**, each crystal of naproxen sodium may optionally be coated with excipient. Tablets may include microcrystalline cellulose and magnesium stearate. For. . . Opadry.RTM. YS-1-4215 (trademarks of Colorcon, West Point, Pa.). Povidone and talc may also be used as bulking agents for the **tablet** core.

DETD [0072] **Tablet** stability is compromised in instances in which there is an "acid-base incompatibility" between the metoclopramide and the analgesic. For example,. . . The basic salt of metoclopramide intimately mixed with acidic naproxen sodium crossreacts in a matter of days causing reduction in **tablet** potency of about 5% in two weeks and about 20 to 25% or more in three weeks at ambient temperature.. . .

DETD Example 2: **Tablet** Formulation #2

DETD [0073] FIG. 2. depicts a sequentially and rapidly dissolving bilayer **tablet** of metoclopramide, 16 mg, combined with naproxen sodium 500 mg. The **tablet** consists of a first layer (11) and a second layer (13). The first layer (11) contains naproxen sodium in crystalline. . . a matrix (17) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "second carrier material"). A pharmaceutically acceptable **tablet** coating (18) surrounds the active ingredients and carrier

materials. Dotted line 15 represents the interface between the two layers which are separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. The first carrier material and the second carrier material may be either the same or different.

DETD Example 3: **Tablet** Formulation #3

DETD [0075] A particular example of a **tablet** in which metoclopramide is in an effervescent matrix separated from analgesic is as follows:

DETD . . . Naproxen: 500 mg of naproxen sodium are compacted as granules with: povidone k-29/32 (23.6 mg); microcrystalline cellulose, NF (105.9 mg); **croscarmellose** sodium, NF, (13.5 mg); talc (27 mg); and magnesium stearate (5 mg).

DETD [0078] C. The metoclopramide granules and the naproxen are combined into a two-layer **tablet** as described in Example 2.

DETD Example 4: **Tablet** Formulation #4

DETD [0079] FIG. 3. depicts another example of a sequentially and rapidly dissolving bilayer **tablet** in which metoclopramide hydrochloride (8 mg) is combined with naproxen sodium (500 mg). Referring to the figure, the bilayer **tablet** consists of a first layer (311) and a second layer (313) having an exterior portion (317) and an interior portion. . . crystalline form 314) uniformly distributed throughout the exterior portion of layer (313), wherein (317) comprises a matrix of pharmaceutically acceptable **tablet** coating. A **tablet** coating (317) surrounds both the second layer as well as the layer of naproxen and carrier material (311). Dotted line. . .

DETD . . . The naproxen-containing portion of tablets may be separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. It is then spray coated with a material absent metoclopramide, e.g., HPMC, triethyl citrate, and TiO₂ applied in. . .

DETD [0081] Preparation of a **tablet** of FIG. 3 requires particular attention to the application of metoclopramide in such a manner as to maintain acceptable **tablet** dosage uniformity ("uniform-coated unit dosage form"). Coating should be uniform to between 85% and 115% of the intended dosage with. . . deviation of 6.4 or less. With pancoating methodology, it is important to control pan speed, movement of tablets across the **tablet** bed, spray temperature and spray coverage relative to the entire pan. Tablets sticking to each other or to the pan. . .

DETD [0082] FIG. 6 depicts an apparatus for coating tablets. A rotating coating pan (602) is partially filled with **tablet** cores to be coated. In the embodiment shown, screen panels (604) facilitate air circulation, and baffles (608) placed on the coating pan walls agitate **tablet** cores during rotation. Spray nozzles (612) and (614)) leading from a spray mixture reservoir, and pump means spray coating through an inlet (610) over **tablet** cores. An air source (618) introduces drying air into the coating pan from a heating and pumping source (not shown).. . .

DETD . . . Franklin Park Ill.)). Using two spray guns about 10 to 12 inches apart and 4 to 8 inches above the **tablet** bed should produce a suitable coating when pans are rotated at a speed of 14 to 16 rpm. It is particularly important to maintain **tablet** movement in the pan to avoid **tablet** sticking and enhance coating uniformity.

DETD Example 5: **Tablet** Formulation #5 (Metoclopramide film coated **tablet**)

DETD [0084] This acid-base storage stable uniform-coated unit dosage form has metoclopramide as a film in the outermost portion of the **tablet** and separated from the naproxen sodium. The final **tablet** formulation by weight is as follows:

- A. metoclopramide hydrochloride 8 mg
- (i) metoclopramide-containing coating (in percentage of total. . . citrate 0.1% .+- . 0.5%
- metoclopramide 26% .+- . 1%
- talc 24% .+- . 1%
- (ii) metoclopramide free coating (in percentage of total **tablet** dry weight)
- hydroxypropyl methylcellulose 9%
- titanium dioxide 1%
- triethyl citrate 2%

- B. naproxen core
- naproxen sodium 500 mg
- povidone k-29/32 23.6 mg
- microcrystalline cellulose, NF, 105.9 mg
- croscarmellose** sodium, NF 13.5
- talc 27 mg
- magnesium stearate 5 mg

DETD [0085] To prepare a two layer **tablet** as in FIG. 3., particular attention is paid to the application of the film coating. Naproxen cores are placed in. . . 14-16 rpm. From two spray guns mounted about 4 to 8 inches apart and 10 to 12 inches above the **tablet** bed, atomized metoclopramide-free coating mixture is sprayed over the rotating pan until the cores increase from about 2% to about. . .

DETD . . . step, tablets are again spray coated in the rotating baffled pan, but now with a metoclopramide-containing coating material until the **tablet** weight increases from about 8 to about 10% over the weight of the naproxen core. For example, sufficient spraying may be performed to apply 8 mg of metoclopramide to each **tablet**.

DETD . . . "uniform-coated unit dosage form." Testing the content of metoclopramide HCl should confirm that the metoclopramide in the coating of each **tablet** is between 85% and 115% of the calculated dosage with a standard deviation of no more than 6.4.

DETD Example 6: Examination of **Tablet** Dissolution Time

DETD . . . from the oral dosage form was observed within about 5 minutes (using 0.01 M to 0.1 M HCl) for the **tablet** of Example 4.

DETD . . . attack with typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a single oral (single layer) **tablet** containing metoclopramide (8 mg) and naproxen sodium (250 mg). Her symptoms start to diminish within one hour and, by three. . .

DETD . . . attack with typical symptoms: migraine headache, nausea and sensitivity to light and sound. She is administered a single oral (bilayer) **tablet** containing metoclopramide (16 mg) and naproxen sodium (500 mg). Her symptoms start to diminish within one hour. By three hours,. . .

DETD . . . Example 7 and 8 are presented by a male, 25 years of age. Upon oral administration of a single layer **tablet** containing 16 mg of metoclopramide and 1000 mg naproxen sodium the same result is obtained.

DETD . . . of a migraine attack consisting of typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a **tablet** prepared according to Example 5 containing metoclopramide (8 mg) and naproxen sodium (500 mg). The naproxen moves from the stomach. . .

DETD . . . shown in Table 2, this was demonstrated based on a comparison of plasma naproxen levels for a single MT 100 **tablet** vs. those for the **tablet** containing naproxen sodium alone. The presence of metoclopramide resulted in an earlier Tmax (by approximately 30 minutes) and a slightly. . .

CLM What is claimed is:

2. The pharmaceutical composition of claim 1, wherein said unit dosage

form is a **tablet** or capsule.

13. The pharmaceutical composition of claim 11, wherein said unit dosage form is a **tablet** or capsule.

. . . The pharmaceutical composition of claim 13, wherein said metoclopramide and said analgesic are each in separate layers of a multilayer **tablet**.

22. The pharmaceutical composition of claim 21, wherein said unit dosage form is a **tablet** or capsule.

. . . 23. The pharmaceutical composition of claim 22, wherein said metoclopramide and said analgesic are in separate layers of a multilayer **tablet**.

38. The pharmaceutical composition of claim 37, wherein said unit dosage form is a **tablet** or capsule.

41. The pharmaceutical composition of claim 29, wherein said unit dosage form is a multilayer **tablet**.

46. The pharmaceutical composition of claim 45, wherein said unit dosage form is a **tablet** or capsule.

IT 53-86-1, Indomethacin 61-68-7, Mefenamic acid 364-62-5,
Metoclopramide 5104-49-4, Flurbiprofen 7232-21-5, Metoclopramide
hydrochloride 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen
22204-53-1, Naproxen 26159-34-2, Naproxen sodium 36322-90-4,
Piroxicam **41340-25-4**, Etodolac 42924-53-8, Nabumetone
74103-06-3, Ketorolac
(metoclopramide and NSAIDs for treatment of migraine headache)

L3 ANSWER 7 OF 9 USPTAFULL on STN

AB The invention is directed to pharmaceutical compositions useful in the treatment of migraine. The compositions contain metoclopramide and one or more NSAIDs in unit dosage form. By selecting NSAIDs that are non-acidic or segregating the metoclopramide and NSAID, the storage life of the compositions has been increased. Also disclosed are coordinated dosage forms for the sequential release of drugs. The invention encompasses methods of treating migraine using any of these dosage forms.

SUMM . . . non-acidic NSAID) in an amount effective to reduce or eliminate headache pain. Preferably, the dosage form should be either a **tablet** or capsule and should be free from vasoactive agents, including 5 HT agonist vasoactive agents. The dosage form may be. . .

SUMM . . . which either metoclopramide or analgesic is barrier coated. Alternatively, metoclopramide and analgesic may be in separate layers of a multilayer **tablet**. Dosage forms should typically be free of vasoactive agents, may be coordinated and may contain either long-acting NSAIDs or NSAIDs. . . .

SUMM . . . (1999), ISBN: 0471148288). Coordinated dosage forms should be suitable for oral delivery and will typically take the form of a **tablet** or capsule. Metoclopramide and NSAID may be in separate layers of a multilayer **tablet** and, in general, these dosage forms should be substantially free of vasoactive agents such as 5 HT agonists.

SUMM . . . be acid-base storage stabilized or coordinated and should, preferably, be suitable for oral administration (e.g. in the form of a **tablet** or capsule). It will also generally be advantageous for metoclopramide to be present at a concentration effective to reduce or. . .

DRWD FIG. 4. is a comparative dissolution plot of the metoclopramide presented in a **tablet** coating layer and presented in a compressed **tablet** layer.

DRWD FIG. 5a is a plot of plasma concentrations of metoclopramide upon administration of **tablet(s)** of the present invention as disclosed in **Tablet** Example 4.

DRWD FIG. 5b is a plot of plasma concentrations of naproxen sodium upon administration of **tablet(s)** of the present invention as disclosed in **Tablet** Example 4.

DRWD FIG. 6 is a diagrammatic cross section side view of a **tablet** coating pan with baffles and spray nozzles.

DETD . . . that serves as a barrier to prevent interaction or the drugs may be segregated into different layers of a multilayer **tablet**. Methods for producing "acid-base storage stabilized" dosage forms are described in the Examples section below. Such dosage forms may, of. . .

DETD The Making of **Tablet** Dosage Forms

DETD The combination of metoclopramide and an analgesic may take place in a single layer **tablet** or other solid dosage form. A bi- or multi layer **tablet** of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the. . .

DETD In a bilayer configuration, one portion of the **tablet** contains metoclopramide in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc., and is, preferably, designed. . . the naproxen (or other analgesic) to the small intestine which is the site of most rapid absorption. In a bilayer **tablet** embodiment, the second portion of the **tablet** will contain, preferably, naproxen sodium in the required dose and appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. It. . .

DETD In one embodiment of bilayer **tablet** preparation, once the two components have been manufactured, they are combined into a single **tablet**. This process allows for different dosages of either component (i.e. the metoclopramide component or the naproxen sodium component) to be usefully combined into a single **tablet** in an efficient way. In another embodiment, substantially each naproxen sodium crystal (or metoclopramide particle) is coated with a rapid. . .

DETD Powder flow characteristics and powder compressibility are the main criteria to be considered with respect to successful **tablet** production. To improve compressibility, naproxen sodium may be granulated. This involves increasing granule size through the addition of excipients that. . .

DETD . . . forms should be used, e.g., the acidic analgesic and the metoclopramide may be sequestered to different layers of a multilayer **tablet** in such a manner that contact between the drugs is eliminated or minimized. In the case of COX-2 inhibitors, the. . .

DETD . . . al., Jpn. J. Pharmacol. 78:365-371 (1998); and Panara, et al., Br. J. Pharmacol. 116:2429-2434 (1995). The amount present in a **tablet** or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example, piroxicam may be present at 10 to 20 mg per **tablet**. Celecoxib may be administered to a human in an amount of from about 100 mg to about 500 mg or. . .

DETD N. "Unit dosage form" shall mean single drug administration entity. By way of example, a single **tablet**, capsule, dragee, or trochee (oral unit dosage forms), suppository, or syringe combining both metoclopramide and an NSAID would be a. . .

DETD . . . levels of metoclopramide. The data was obtained from 10 healthy volunteer subjects. On day 1, the subjects were administered one **tablet** of 500 mg naproxen sodium and 8 mg metoclopramide prepared as described in the Examples section. On day 4, two. . .

DETD **Tablet Formulation #1**

DETD A variety of combinations of metoclopramide and analgesic can be made into a single dosage form (e.g., **tablet**, capsule, suppository) consisting of one or more layers. In this example, a sequentially and rapidly dissolving single layer **tablet** of metoclopramide, 8 mg, is combined with naproxen sodium, 500 mg. Referring to FIG. 1, this single layer **tablet** contains naproxen sodium in crystalline form (2) and metoclopramide (4), each uniformly distributed throughout a matrix (6) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "carrier material"). A pharmaceutically acceptable **tablet** coating (8) surrounds the active ingredients and carrier materials. Carrier material should be present in an amount of between 50 and 2000 mg, and preferably between 500 and 1,000 mg. Prior to compaction in a **tablet**, each crystal of naproxen sodium may optionally be coated with excipient. Tablets may include microcrystalline cellulose and magnesium stearate. For. . . YS- 1-4215 (trademarks of Colorcon, West Point, Pa.). Povidone and talc may also be used as bulking agents for the **tablet** core.

DETD **Tablet** stability is compromised in instances in which there is an "acid-base incompatibility" between the metoclopramide and the analgesic. For example,. . . The basic salt of metoclopramide intimately mixed with acidic naproxen sodium crossreacts in a matter of days causing reduction in **tablet** potency of about 5% in two weeks and about 20 to 25% or more in three weeks at ambient temperature.. . .

DETD **Tablet Formulation #2**

DETD FIG. 2. depicts a sequentially and rapidly dissolving bilayer **tablet** of metoclopramide, 16 mg, combined with naproxen sodium 500 mg. The **tablet** consists of a first layer (11) and a second layer (13). The first layer (11) contains naproxen sodium in crystalline. . . a matrix (17) of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants (collectively, "second carrier material"). A pharmaceutically acceptable **tablet** coating (18) surrounds the active ingredients and carrier materials. Dotted line 15 represents the interface between the two layers which are separately molded, poured, compressed or otherwise formed and joined by compression or other **tablet** forming means. The first carrier material and the second carrier material may be either the same or different.

DETD **Tablet Formulation #3**

DETD A particular example of a **tablet** in which metoclopramide is in an effervescent matrix separated from analgesic is as follows:

DETD . . . Naproxen: 500 mg of naproxen sodium are compacted as granules with: povidone k-29/32 (23.6 mg); microcrystalline cellulose, NF (105.9 mg); **croscarmellose** sodium, NF, (13.5 mg); talc (27 mg); and magnesium stearate (5 mg).

DETD C. The metoclopramide granules and the naproxen are combined into a two-layer **tablet** as described in Example 2.

DETD **Tablet Formulation #4**

DETD FIG. 3. depicts another example of a sequentially and rapidly dissolving bilayer **tablet** in which metoclopramide hydrochloride (8 mg) is combined with naproxen sodium (500 mg). Referring to the figure, the bilayer **tablet** consists of a first layer (311) and a second layer (313) having an exterior portion (317) and an interior portion. . . crystalline form (314) uniformly distributed throughout the exterior portion of layer (313), wherein (317) comprises a matrix of pharmaceutically acceptable **tablet** coating. A **tablet** coating (317) surrounds both the second layer as well as the layer of naproxen and carrier material (311). Dotted line. . .

DETD The naproxen-containing portion of tablets may be separately molded, poured, compressed or otherwise formed and joined by compression or

other **tablet** forming means. It is then spray coated with a material absent metoclopramide, e.g., HPMC, triethyl citrate, and TiO₂ applied in. . .

DETD Preparation of a **tablet** of FIG. 3 requires particular attention to the application of metoclopramide in such a manner as to maintain acceptable **tablet** dosage uniformity ("uniform-coated unit dosage form"). Coating should be uniform to between 85% and 115% of the intended dosage with. . . deviation of 6.4 or less. With pancoating methodology, it is important to control pan speed, movement of tablets across the **tablet** bed, spray temperature and spray coverage relative to the entire pan. Tablets sticking to each other or to the pan. . .

DETD FIG. 6 depicts an apparatus for coating tablets. A rotating coating pan (602) is partially filled with **tablet** cores to be coated. In the embodiment shown, screen panels (604) facilitate air circulation, and baffles (608) placed on the coating pan walls agitate **tablet** cores during rotation. Spray nozzles ((612) and (614)) leading from a spray mixture reservoir, and pump means spray coating through an inlet (610) over **tablet** cores. An air source (618) introduces drying air into the coating pan from a heating and pumping source (not shown)..

DETD . . . Franklin Park Ill.)). Using two spray guns about 10 to 12 inches apart and 4 to 8 inches above the **tablet** bed should produce a suitable coating when pans are rotated at a speed of 14 to 16 rpm. It is particularly important to maintain **tablet** movement in the pan to avoid **tablet** sticking and enhance coating uniformity.

DETD **Tablet** Formulation #5 (Metoclopramide Film Coated **Tablet**)

DETD This acid-base storage stable uniform-coated unit dosage form has metoclopramide as a film in the outermost portion of the **tablet** and separated from the naproxen sodium. The final **tablet** formulation by weight is as follows:

DETD . . . 0.5%
metoclopramide 26% .+-. 1%
talc 24% .+-. 1%
(ii) metoclopramide free coating
(in percentage of total
tablet dry weight)
hydroxypropylmethylcellulose 9%
titanium dioxide 1%
triethyl citrate 2%
B. naproxen core
naproxen sodium 500 mg
povidone k-29/32 23.6 mg
microcrystalline cellulose, NF, 105.9 mg
croscarmellose sodium, NF 13.5
talc 27 mg
magnesium stearate 5 mg

DETD To prepare a two layer **tablet** as in FIG. 3., particular attention is paid to the application of the film coating. Naproxen cores are placed in. . . 14-16 rpm. From two spray guns mounted about 4 to 8 inches apart and 10 to 12 inches above the **tablet** bed, atomized metoclopramide-free coating mixture is sprayed over the rotating pan until the cores increase from about 2% to about. . .

DETD . . . step, tablets are again spray coated in the rotating baffled pan, but now with a metoclopramide-containing coating material until the **tablet** weight increases from about 8 to about 10% over the weight of the naproxen core. For example, sufficient spraying may be performed to apply 8 mg of metoclopramide to each **tablet**.

DETD . . . "uniform-coated unit dosage form." Testing the content of metoclopramide HCl should confirm that the metoclopramide in the coating

of each **tablet** is between 85% and 115% of the calculated dosage with a standard deviation of no more than 6.4.

DETD Examination of **Tablet** Dissolution Time

DETD . . . from the oral dosage form was observed within about 5 minutes (using 0.01 M to 0.1 M HCl) for the **tablet** of Example 4.

DETD . . . attack with typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a single oral (single layer) **tablet** containing metoclopramide (8 mg) and naproxen sodium (250 mg). Her symptoms start to diminish within one hour and, by three. . .

DETD . . . attack with typical symptoms: migraine headache, nausea and sensitivity to light and sound. She is administered a single oral (bilayer) **tablet** containing metoclopramide (16 mg) and naproxen sodium (500 mg). Her symptoms start to diminish within one hour. By three hours, . . .

DETD . . . Example 7 and 8 are presented by a male, 25 years of age. Upon oral administration of a single layer **tablet** containing 16 mg of metoclopramide and 1000 mg naproxen sodium the same result is obtained.

DETD . . . of a migraine attack consisting of typical symptoms: headache, nausea and sensitivity to light and sound. She is administered a **tablet** prepared according to Example 5 containing metoclopramide (8 mg) and naproxen sodium (500 mg). The naproxen moves from the stomach. . .

DETD . . . shown in Table 2, this was demonstrated based on a comparison of plasma naproxen levels for a single MT 100 **tablet** vs. those for the **tablet** containing naproxen sodium alone. The presence of metoclopramide resulted in an earlier Tmax (by approximately 30 minutes) and a slightly. . .

CLM What is claimed is:

7. The pharmaceutical composition of claim 6, wherein said unit dosage form is a **tablet** or capsule.

. . . 8. The pharmaceutical composition of claim 7, wherein said metoclopramide and said analgesic are in separate layers of a multilayer **tablet**.

23. The pharmaceutical composition of claim 22, wherein said unit dosage form is a **tablet** or capsule.

32. The pharmaceutical composition of either claim 30 or claim 31, wherein said unit dosage form is a **tablet** or capsule.

. . . acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer **tablet**.

IT 53-86-1, Indomethacin 103-90-2, Acetaminophen 5104-49-4, Flurbiprofen 15687-27-1, Ibuprofen 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 36322-90-4, Piroxicam **41340-25-4**, Etodolac 42924-53-8, Nabumetone 71125-38-7, Meloxicam 74103-06-3, Ketorolac 123653-11-2, NS398 158205-05-1, L-745337 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 180200-68-4, JTE-522 (metoclopramide and NSAID for treatment of migraine headache)

L3 ANSWER 8 OF 9 USPTAFULL on STN

AB The present invention provides solid pharmaceutical compositions for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic

surfactants and triglycerides. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compositions of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutrionals, cosmeceuticals and diagnostic agents.

DETD . . . bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a minitab^{let}, a **tablet** or a capsule. A powder constitutes a finely divided (milled, micronized, nanosized, precipitated) form of an active ingredient or additive. . . .

DETD disintegrants or super disintegrants, such as **croscarmellose** sodium, starch, starch derivatives, clays, gums, cellulose, cellulose derivatives, alginates, crosslinked polyvinylpyrrolidone, sodium starch glycolate and microcrystalline cellulose;

DETD . . . other processes known in the art. The compositions can be provided in the form of a minicapsule, a capsule, a **tablet**, an implant, a troche, a lozenge (minitab^{let}), a temporary or permanent suspension, an ovule, a suppository, a wafer, a chewable **tablet**, a quick or fast dissolving **tablet**, an effervescent **tablet**, a buccal or sublingual solid, a granule, a film, a sprinkle, a pellet, a bead, a pill, a powder, a. . . .

DETD . . . or otherwise added to the carrier or composition. The coating may be applied to a compressed or molded or extruded **tablet**, a gelatin capsule, and/or pellets, beads, granules or particles of the carrier or composition. The coating may be applied through. . . .

DETD . . . effect release in the lower gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded **tablet**/mold (coated or uncoated) containing granules, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves. . . .

DETD . . . (morphology, particle size distribution, polymorphism and dissolution characteristics) of spray congealed pellets. The spray congealed particles may be used in **tablet** granulation form, encapsulation form, or can be incorporated into a liquid suspension form.

CLM What is claimed is:

. . . pellet, a bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a **tablet** and a capsule.

. . . composition of claim 1 in the form of a capsule, a table, an ovule, a suppository, a water, a chewable **tablet** a buccal **tablet**, a sublingual **tablet**, a quick-dissolved **tablet**, an effervescent **tablet**, a granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitutable solid,. . . .

52. The pharmaceutical composition of claim 6 in the form of a capsule, a **tablet**, an ovule, a suppository, a wafer, a chewable **tablet**, a buccal **tablet**, a sublingual **tablet**, a quick-dissolve **tablet**, an effervescent **tablet**, a granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitutable solid,. . . .

IT 50-14-6, Ergocalciferol 50-21-5D, Lactic acid, glycerides 50-24-8, Prednisolone 50-28-2, EStradiol, biological studies 50-70-4, Sorbitol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 55-98-1, Busulphan 56-81-5, 1,2,3-Propanetriol, biological studies 56-81-5D, Glycerol, polyethylene fatty acid esters 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 57-55-6,

1,2-Propanediol, biological studies 57-55-6D, Propylene glycol, ethers
 57-83-0, Progesterone, biological studies 57-88-5, Cholesterol,
 biological studies 57-88-5D, Cholesterol, polyoxyethylene derivs.
 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies
 64-17-5, Ethanol, biological studies 66-76-2, Dicoumarol 67-20-9,
 Nitrofurantoin 67-45-8, Furazolidone 67-63-0, Isopropanol, biological
 studies 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol
 69-65-8, Mannitol 71-36-3, Butanol, biological studies 76-57-3,
 Codeine 76-99-3, Methadone 77-89-4, Acetyl triethylcitrate 77-90-7,
 Acetyl tributyl citrate 77-92-9D, Citric acid, diglycerides 77-93-0,
 Triethylcitrate 77-94-1, Tributylcitrate 81-24-3 81-25-4 83-44-3
 87-33-2, Isosorbide dinitrate 87-69-4D, Tartaric acid, glycerides,
 biological studies 90-82-4, Pseudoephedrine 100-51-6,
 Benzenemethanol, biological studies 102-76-1, Triacetin 104-31-4,
 Benzonatate 105-37-3, Ethyl propionate 105-54-4, Ethyl butyrate
 105-60-2, biological studies 105-60-2D, Caprolactam, N-Alkyl derivs.
 106-32-1, Ethyl caprylate 107-21-1, 1,2-Ethanediol, biological studies
 110-27-0, Isopropyl myristate 111-03-5, Glyceryl monooleate 111-62-6,
 Crodamol EO 111-90-0, Transcutol 112-80-1, 9-Octadecenoic acid (9Z)-,
 biological studies 113-15-5, Ergotamine 113-92-8, Chlorpheniramine
 115-77-5, biological studies 115-83-3, Pentaerythrityl Tetra stearate
 124-07-2, Octanoic acid, biological studies 125-84-8, Aminogluthethimide
 126-07-8, Griseofulvin 127-19-5, Dimethylacetamide 128-13-2
 141-22-0 142-18-7, Glyceryl monolaurate 142-62-1, Hexanoic acid,
 biological studies 142-91-6, Isopropyl palmitate 143-07-7, Dodecanoic
 acid, biological studies 151-41-7, Lauryl sulfate 155-97-5,
 Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide
 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amphetamine
 302-79-4, Tretinoin 303-49-1, Clomipramine 321-64-2, Tacrine
 334-48-5, Decanoic acid 359-83-1, Pentazocine 360-65-6 378-44-9,
 Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1,
 Metronidazole 463-40-1 474-25-9 475-31-0 511-12-6,
 Dihydroergotamine 516-35-8 516-50-7 520-85-4, Medroxyprogesterone
 542-28-9, .delta.-Valerolactone 544-35-4, Ethyl linoleate 544-63-8,
 Tetradecanoic acid, biological studies 577-11-7, Sodium docusate
 595-33-5 616-45-5, Pyrrolidone 616-45-5D, Pyrrolidone, N-Alkyl
 derivs. 623-84-7, Propylene glycol diacetate 640-79-9 675-20-7,
 2-Piperidone 872-50-4, N-Methylpyrrolidone, biological studies
 1134-47-0, Baclofen 1331-12-0, Propylene glycol monoacetate
 1335-71-3, Propylene glycol oleate 1338-39-2, Arlacel 20 1338-43-8,
 Span 80 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4,
 Vitamin E 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol
 2687-91-4, N-Ethylpyrrolidone 2687-94-7 2687-96-9 3068-88-0,
 .beta.-Butyrolactone 3445-11-2 4419-39-0, Beclomethasone 4759-48-2,
 Isotretinoin 5104-49-4, Flurbiprofen 5306-85-4, Dimethyl isosorbide
 7261-97-4, Dantrolene 7488-99-5, .alpha. Carotene 7664-93-9D,
 Sulfuric acid, salts alkyl derivs., biological studies 7689-03-4,
 Camptothecin 8007-43-0, Sorbitan sesquioleate 9002-89-5,
 Polyvinylalcohol 9002-92-0, Brij 30 9002-96-4 9003-39-8,
 Polyvinylpyrrolidone 9004-65-3, Hydroxypropyl methylcellulose
 9004-74-4, Methoxy polyethylene glycol 9004-81-3, Polyoxyethylene
 laurate 9004-95-9, Polyoxyethylene cetyl ether 9004-96-0, PEG-32
 oleate 9004-98-2, Polyoxyethylene oleyl ether 9004-99-3,
 Polyoxyethylene stearate 9005-00-9, Polyoxyethylene stearyl ether
 9005-02-1, Polyoxyethylene dilaurate 9005-07-6, Polyoxyethylene
 dioleate 9005-08-7, Polyoxyethylene distearate 9005-32-7D, Alginic
 acid, salts 9005-37-2, Propylene glycol alginate 9005-63-4D,
 Polyoxyethylene sorbitan, derivs. 9005-63-4D, Polyoxyethylene sorbitan,
 fatty acid esters 9005-64-5, Tween 20 9005-65-6, Polysorbate 80
 9005-66-7, Tween 40 9005-67-8, Tween 60 9007-48-1, PLUROLIOLEIQUECC497
 9011-21-6, Polyoxyethylene glyceryl stearate 9016-45-9 9036-19-5
 10238-21-8, Glyburide 10540-29-1, Tamoxifen 11103-57-4, Vitamin A

11140-04-8, Imwitor 988 12001-79-5, Vitamin K 12619-70-4,
 Cyclodextrin 12619-70-4D, Cyclodextrin, derivs. 12619-70-4D,
 Cyclodextrin, hydroxypropyl ethers 13081-97-5, Pentaerythrityl di
 stearate 14440-80-3, Stearoyl-2-lactylate 14605-22-2 15307-86-5,
 Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 15687-27-1,
 Ibuprofen 18559-94-9, Albuterol 19356-17-3, Calcifediol 20594-83-6,
 Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4,
 Nifedipine 22882-95-7, Isopropyl linoleate 22916-47-8, Miconazole
 23288-49-5, Probuco1 25168-73-4, Sucrose monostearate 25265-75-2,
 Butanediol 25322-68-3 25322-69-4, Polypropylene glycol 25339-99-5,
 Sucrose monolaurate 25523-97-1, Dexchlorpheniramine 25618-55-7D,
 Polyglycerol, fatty acid esters 25637-84-7, Glyceryl dioleate
 25637-97-2, Sucrose dipalmitate 25812-30-0, Gemfibrozil 26266-57-9,
 Sorbitan monopalmitate 26266-58-0, Sorbitan Trioleate 26402-22-2,
 Glyceryl monocaprate 26402-26-6, Glyceryl monocaprylate 26446-38-8,
 Sucrose monopalmitate 27154-43-4D, Piperidone, N-Alkyl derivs.
 27195-16-0, Sucrose distearate 27203-92-5, TRamadol 27638-00-2,
 Glyceryl dilaurate 29094-61-9, Glipizide 29767-20-2, Teniposide
 31692-85-0, Glycofuro1 32222-06-3, Calcitriol 33069-62-4, Paclitaxel
 33419-42-0, Etoposide 34911-55-2, Bupropion 36354-80-0, Glyceryl
 dicaprylate 37321-62-3, Lauroglycol 38304-91-5, Minoxidil
41340-25-4, Etodolac 42924-53-8, Nabumetone 43200-80-2,
 Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone
 51333-22-3, Budesonide 51481-61-9, Cimetidine 51938-44-4, Sorbitan
 sesquistearate 52581-71-2, Volpo 3 53123-88-9, Sirolimus
 53168-42-6, Myvacet 9-45 53179-11-6, Loperamide 53230-10-7,
 Mefloquine 53988-07-1, Glyceryl dicaprate 54392-26-6, Sorbitan
 monoisostearate 54965-21-8, Albendazole 55079-83-9, Acitretin
 55142-85-3, Ticlopidine 57107-97-8, Polyoxyethylene glyceryl oleate
 59467-70-8, Midazolam 59865-13-3, Cyclosporine 60142-96-3, Gabapentin
 61379-65-5, Rifapentine 61869-08-7 62013-04-1, Dirithromycin
 62356-64-3 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9,
 Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole
 68506-86-5, Vigabatrin
 (pharmaceutical compns. and methods for improved delivery of
 hydrophobic therapeutic agents)

L3 ANSWER 9 OF 9 USPATFULL on STN

AB Dispersible particles consisting essentially of crystalline NSAID having
 hydroxypropyl cellulose adsorbed on the surface thereof in an amount
 sufficient to maintain an effective average particle size of less than
 about 1000 nm. Pharmaceutical compositions containing the particles
 exhibit unexpectedly reduced gastric irritation following oral
 administration and/or hastened onset of action.

DETD . . . strength of 250 mg naproxen/capsule. 220 g of the spray dried
 material above was blended prepared with 44 g of **croscarmellose**
 sodium (Ac-Di-Sol) in a small twin shell blender. The material was
 passed through a roller compactor at 10 tons pressure. . . blended
 with the dry granulation for 15 minutes in a twin shell blender. The
 powder was compressed on a rotary **tablet** press to a final
tablet weight of 400 mg and a hardness of 9-12 kp. Each
tablet contained 200 mg of naproxen. The nanonaproxoflin was
 tested for adsorption time spiral co? tablets in fed dogs. The
 following. . .

IT 50-33-9, Phenylbutazone, biological studies 50-78-2, Aspirin 53-86-1,
 Indomethacin 61-68-7, Mefenamic acid 80-08-0, Dapsone 129-20-4,
 Oxyphenbutazone 530-78-9, Flufenamic acid 644-62-2, Meclofenamic acid
 2438-72-4, Bufexamac 4394-00-7, Niflumic acid 5003-48-5, Benorylate
 5104-49-4, Flurbiprofen 6064-83-1, Fosfosal 9004-64-2, Hydroxypropyl
 cellulose 13539-59-8, Apazone 15307-86-5, Diclofenac 15687-27-1,
 Ibuprofen 18046-21-4, Fentiazac 18694-40-1, Epirizole 21256-18-8,
 Oxaprozin 22071-15-4, Ketoprofen 22131-79-9, Alclofenac 22204-53-1,

Naproxen 22494-42-4, Diflunisal 22760-18-5, Proquazone 24237-54-5,
Tinoridine 26171-23-3, Tolmetin 29679-58-1, Fenoprofen 30748-29-9,
Feprazone 31793-07-4, Pirprofen 31842-01-0, Indoprofen 32527-55-2,
Tiaramide 33005-95-7, Tiaprofenic acid 34042-85-8, Sudoxicam
34552-84-6, Isoxicam 34645-84-6, Fenclofenac 36322-90-4, Piroxicam
36330-85-5, Fenbufen 36740-73-5, Flumizole 38194-50-2, Sulindac
40828-46-4, Suprofen **41340-25-4**, Etodolac 42924-53-8,
Nabumetone 53716-49-7, Carprofen 58433-11-7, Tilomisole 59804-37-4,
Tenoxicam 71079-19-1, Timegadine
(nonsteroidal anti-inflammatory nanoparticles modified with
hydroxypropyl cellulose)